RARECARE

Surveillance of Rare Cancers in Europe

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D 15 - Report with quality considerations on the available data on rare cancers

Prepared by:

Carmen Martinez, Gemma Gatta, Annalisa Trama, Riccardo Capocaccia, Maria-José Sánchez-Pérez, Juan-Manuel Melchor

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Introduction

During the last 40 years population-based Cancer Registries (CRs) have contributed data to Cancer Incidence in Five Continents, and to other collaborative European projects such as EUROCARE (Survival of cancer patients in Europe http://www.eurocare.it/). This collaboration has contributed to set common criteria and rules to improve the quality and comparability of data among CRs. However, when data are used for specific purposes, such as for studying tumours with uncommon morphology types, a more careful validation is established. For new studies it is not uncommon to highlight residual problems in data quality and standardisation.

On the basis of past experience of the analysis on rare cancers [1], data quality for rare cancers doesn't seem as good as that for non rare tumours. The major reason is that rare tumour entities, as defined by the RARECARE project, are a combination of International Classification of Diseases for Oncology, 3rd Edition (ICD-O3) topography and morphology codes. Sometimes although topography is detailed to the 4th digit (sub-site) and morphology codes refer to a rare morphology, there are still well known problems in diagnostic accuracy. An additional difficulty is due to the changes of the ICD-O classification. The inclusion of new morphology and topography codes has forced registries to update not only the new but also the old data leading to additional efforts and raising comparability issues.

For these reasons, additional work was planned in RARECARE to further study the quality of data of rare tumours.

Objectives

RARECARE aims at estimating the burden of rare malignant tumours in Europe using population based CRs data. One of the aims of the project is to improve data quality in rare cancers registration. The specific objectives follow:

- to assess validity, completeness and standardisation of cancer registries data on rare cancers between registries

- to define recommendations for improving data quality of rare cancers

The improvement of the quality of data will consequently improve the comparability of incidence, prevalence and survival of rare cancers among European population-based CRs.

Methodology

Data quality analysis of the RARECARE database

RARECARE gathered data on cancer patients diagnosed from 1978 to 2002 in 21 European countries, and archived in population-based CRs all of which had vital status information available up to at least 31st December 2003. For 11 countries, the CRs covered the entire national population (Austria, Iceland, Ireland, Malta, Norway, Slovakia, Slovenia, Sweden, Northern Ireland, Scotland and Wales); the other countries do not have national cancer registration and were represented by regional CRs covering variable proportions of their national populations.

Automated procedures checked each data field and combinations of fields in each case record. Topographies and morphologies were checked against ICD-O3 list to identify invalid codes [2; 3]. Other checks were carried out on combinations of data fields. They concerned:

- Consistency between dates of birth, diagnosis and follow-up.
- Consistency of site–morphology combinations. Both, standard IARC routine checks [3] and those additionally defined by the EUROCARE protocol [2; 4] were used.
- Consistency of age–site, age–morphology, sex–site and sex–morphology combinations. Unlikely combinations were checked against IARC criteria [3].
- Consistency of morphology–behaviour combinations.

A more detailed description of the procedure of the data quality check is available in the paper by De Angelis et al [4].

Standard data quality indicators (percentage of autopsies, percentage of Death Certificate Only cases (DCO), percentage of microscopically verified cases, percentage of cases with bases of diagnosis unknown and percentage of cases 1995-1998 censored before 5-year) were calculated to assess the quality of the RARECARE data. Furthermore, 2 possible criteria were identified for testing the quality of the RARECARE data:

1. proportion of cases with generic diagnosis and consequently codified with a nonspecific morphology code, and
2. unexpectedly low incidence of rare tumours, suggesting insufficient specificity of diagnosis.

Estimation of incidence rates can be biased by the inclusion of CRs with insufficient quality of morphological information on diagnoses. In these registries, specific rare tumours may not be precisely recognized and a certain number of patients may have their cancer classified within a wider, not clearly specified category (such as carcinoma NOS, lymphoma NOS, etc).

For each CR, the proportion of cases with non specified morphology and topography was calculated using the following morphology and topography codes. Morphology codes: 8000 (neoplasm, malignant), 8001 (tumour cells, malignant); topography codes: C140, C260, C268, C269, C390, C398, C399, C559, C579, C639, C689, C729, C759-C765, and C767-C768.

Data quality study on a sample of rare tumours

Previous experiences demonstrated that the revision of the pathological reports can improve the quality of the morphology and of the topography. Thus, in addition to the assessment of the main quality indicators traditionally used for CRs, RARECARE undertook a study aimed at assessing the data quality for rare cancers through the revision of reports available at CRs offices.

The specific objectives of the data quality study were: 1) to verify the diagnostic accuracy, 2) to assess the completeness of incidence and 3) to verify the quality of follow-up.

The study focused on a selected sub-group of rare tumours. These tumours were selected because of their relevance for primary prevention, early diagnosis, diagnostic accuracy, quality of care, clinical research feasibility or because of their poor data quality in rare cancer registration (Table 1).

Table 1. Rare tumours included in the data quality study and reasons for their relevance.

Rare tumour	Primary prevention	Early diagnosis	Diagnostic accuracy	Quality of care	Clinical research feasibility	Poor data quality
Mesothelioma	**+++**	?	++	+	++	+
Liver angiosarcoma	**+++**	?	++	++	+	+
Sarcomas	++	++	**+++**	++	+	++
Oral cavity tumours	++	**+++**	+	++	++	+
CNS tumours	++	++	++	**+++**	++	++
Germ cell tumours	+	+	+	**+++**	+	+
Leukaemia	++	+	++	**+++**	+	++
Endocrine tumours	+	?	++	++	++	**+++**

+++ very high relevance, ++ high relevance; + relevant; ? no data on the efficacy

For the revision of the morphology and/or of the primary cancer site, the documents revised were the pathologic reports and the clinical dossiers **filed at cancer registry offices**. If necessary and feasible also the original medical records available at the hospital was retrieved.
Pathological reports were used also to check the availability of information on the stage of the tumours. The CRs internal dossiers of the case were reviewed to verify the availability of information on treatment and place of treatment.

The mortality and population files were reviewed **only** for mesothelioma, angiosarcoma of liver and central nervous system tumours in order to check the vital status.
The period of diagnosis of cases revised was 1995-2002. The study focused on malignant tumours only (5th digit of the morphology codes ≥3).

In addition to the revision undertaken by CRs, standard data quality indicators (percentage of autopsies, percentage of DCO, percentage of microscopically verified cases, percentage of cases with bases of diagnosis unknown and percentage of cases 1995-1998 censored before 5-year) were calculated to assess the quality of the RARECARE data for the selected tumours included in the data quality study.

The criteria used for the selection of CRs were geographic representation and incidence and survival variability. However, all CRs participating in the RARECARE project were invited to join this exercise. Thirty-eight CRs from 13 European countries participated to the data quality study (Table 2).

Table 2. Cancer Registries participating to the RARECARE data quality study and tumours reviewed by CR.

Countries	Registries	Central nervous system	Gonadal germ cell	Leukemia	Liver angiosarcoma	Malignant digestive endocrine	Mesothelioma	Oral cavity	Sarcomas
Austria	Austria	√	√	√	√	√	√	√	√
Belgium	Flemish	√	√	√	√	√	√	√	√
Estonia	Estonia	√	√	-	√	-	√	√	√
France	Côte d'Or Dig.	-	-	-	√	√	-	-	-
	Côte d'Or Hem	-	-	√	-	-	-	-	-
Ireland	Ireland	√	√	√	√	√	√	√	√
Italy	Alto Adige	√	√	√	√	√	√	√	√
	Biella	√	√	√	√	√	√	√	√
	Ferrara	√	√	√	√	√	√	√	√
	Firenze	√	√	√	√	√	√	√	√
	Genoa	√	√	-	√	√	√	√	√
	Modena	√	√	√	√	√	√	√	√
	Napoli	√	√	√	√	√	√	√	√
	Parma	√	√	√	√	√	√	√	√
	Ragusa	√	√	√	√	√	√	√	√
	Reggio Emilia	√	√	√	√	√	√	√	√
	Romagna	-	-	-	-	√	√	-	√
	Trento	√	√	√	√	√	√	√	√
	Varese	√	√	√	√	√	√	√	√
	Veneto	√	√	-	√	√	√	√	√
Malta	Malta	√	√	√	√	√	√	√	√
Netherlands	Amsterdam	√	√	√	√	√	√	√	-
	N. Netherlands	-	-	-	√	√	√	√	√
	Twente	-	-	-	√	√	√	√	√
Poland	Kielce	√	√	√	√	√	√	√	√
	Warsaw	-	√	-	√	√	√	√	√
Slovenia	Slovenia	√	√	√	√	√	√	√	√
Spain	Basque C.	-	√	-	√	-	√	-	-
	Girona	√	√	√	√	√	√	√	√
	Navarra	√	√	√	-	√	√	√	√
	Tarragona	√	√	-	√	-	√	√	√
	Albacete	-	-	-	√	-	-	√	-
	Castilla la M.	√	√	-	√	√	√	√	√
Sweden	Stockholm	√	√	-	√	√	√	√	√
Switzerland	Geneva	√	-	-	-	-	√	-	√
	St. Gallen	-	√	-	√	√	-	-	-
	Ticino	√	√	√	√	√	√	√	√
	Valais	√	√	√	√	√	√	√	√

√ (tumour revised by CR); - (tumour not revised by CR)

Results

Data quality analysis of the RARECARE database

Table 3 shows quality indicators for the data on rare and common cancers archived from 1995 to 2002 by the 76 CRs whose data were used for the RARECARE estimates. The overall proportion of DCO cases was 3%, with only 6 CRs having more than 5% DCO. The overall proportion of cases discovered at autopsy was 0.5%. A high proportion of cases (86% overall) were verified microscopically (MV). Follow-up was complete for most CRs, with follow-up censored before five years in 1.2% of cases overall, with only two CRs having high proportions of cases not followed-up after 2002.

Table 3. Data quality indicators of all malignant tumours diagnosed in European cancer registries included in the analysis, cases diagnosed 1995-2002.

Country	Registry	Number of malignant tumours	Data quality indicators						
			Death certificate only	Autopsy	Microscopic verification	Bases of diagnosis unknown	Cases 1995-1998 censored before five years	Morphology code NOS*	Topography code NOS*
		N	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Austria	Austria	304,493	8.9	0	85.2	13.2	5.9	10.1	0.6
Belgium	Flanders	144,715	0	0.2	89.8	7.8	0	7.3	0.6
France	Bas Rhin	13,113	0	0	95.8	0.1	3.3	3.9	0.5
	Calvados	5,695	0	0	98.1	0.1	6.1	2.5	0.4
	Calvados digestive	2,801	0	0	87	0.7	4.4	10.5	0.3
	Côte d'Or digestive	4,376	0	0	82.8	0.0	0.5	17.5	0.2
	Côte d'Or haematol.	1,884	0	0	100	0.0	7.2	0	0.5
	Doubs	5,742	0	0	95.8	1.0	2.1	3.2	0.3
	Haut Rhin	9,073	0	0	96.4	0.4	5.8	2.9	0.6
	Hérault	10,505	0	0	n.a.	n.a.	6.4	1.5	0.2
	Isère	12,526	0	0	94.1	1.3	4.6	4.1	0.2
	Loire Atlantique	3,746	0	0	100	0.0	6.8	0	0.0
	Manche	6,267	0	0	96.5	0.0	2.7	3.4	0.5
	Marne & Ardennes	168	0	0	100	0.0	3.6	0	0.0
	Somme	6,481	0	0	94.2	1.4	6.6	5.5	1.3
	Tarn	4,935	0	0	93.8	0.1	2	5.9	1.4
Germany	Saarland	54,132	3.9	0	91.8	0.2	5.8	8	0.6
Iceland	Iceland	8,854	0.1	1.4	96.6	0.0	0	3.5	0.0
Ireland	Ireland	156,529	2	0.3	86.7	2.7	0	11	0.7
Italy	Alto Adige	18,676	0.7	0	89.5	0.0	0	9.2	0.5
	Biella	11,770	1.3	0.4	87	1.2	0	12.5	0.4
	Ferrara	23,740	1.1	0	88.1	0.0	0.4	9.7	0.6
	Firenze	66,097	0.9	0.1	80.4	0.0	0.4	17.7	0.8
	Friuli V.G.	78,882	0.6	1.9	91	0.0	0.3	9.8	2.2
	Genoa	44,207	1.8	0	81.4	0.0	0	16.6	1.0
	Macerata	10,396	1.3	0	87.4	0.7	0.2	13.1	0.7
	Modena	34,947	0.5	0	88.6	0.0	0.4	11.8	0.5
	Napoli	8,145	3.9	0	73	0.0	1.9	17.6	1.4
	Palermo	581	2.2	0	92.6	7.4	0	7.2	0.0
	Parma	23,836	1	0	86	0.1	0.3	13.1	0.7
	Ragusa	10,687	1.9	0.8	80.9	1.9	0.1	24.6	0.6
	Reggio Emilia	22,152	0.2	0	88.1	0.0	0	13.8	0.5
	Romagna	60,667	2.4	0	87.9	0.0	0.1	12.3	0.5

	Salerno	26,917	2.5	0	77.5	0.0	4	23.7	1.1
	Sassari	18,084	2.9	0.2	84.4	0.9	0	16.4	0.7
	Trento	17,788	2	0	85	0.0	0.3	27.8	4.0
	Umbria	45,221	0.7	0	84	9.2	0.1	12.6	0.6
	Varese	24,728	1.1	0	89	0.0	11.5	10.8	0.4
	Veneto	84,528	1.5	0.2	87.5	0.0	0.8	13.7	1.9
Malta	Malta	9,848	1.9	0.1	87.6	2.0	0	12.9	0.8
Norway	Norway	197,240	1	0.4	93.1	0.0	0.1	6.7	0.6
Poland	Cracow	24,545	1.1	0.1	75.2	3.6	2.9	27.2	1.2
	Kielce	34,123	0	0	80.2	12.6	0	21.7	1.0
	Warsaw	50,238	3.4	0	80.2	2.2	0.2	19.1	0.8
Portugal	South Portugal	32,917	0	0	93.9	2.0	0	7.2	0.5
Slovakia	Slovakia	128,686	12.8	1.5	81.8	10.8	0.5	17.9	1.7
Slovenia	Slovenia	56,632	1.6	1.1	90.8	1.3	0.1	9.6	0.7
Spain	Albacete	1,941	4.7	0	89.3	6.6	0.3	11.9	0.0
	Basque Country	44,809	4.2	0	86.3	5.2	0.1	11.4	0.7
	Castillon	1,608	4.7	0	95	4.7	0	5.4	0.0
	Girona	19,936	3.8	0.1	87.7	0.6	0.1	12.8	0.7
	Granada	7,298	2.1	0.1	89.3	0.3	0	10.8	0.0
	Murcia	14,068	3.5	0.1	88	5.2	2.5	11.1	1.1
	Navarra	15,381	2.2	0.6	90.9	0.1	0.6	7.6	0.4
	Tarragona	12,412	4.8	0	86.4	5.0	0.1	13.3	0.8
Sweden	Sweden	347,616	0	2.2	98.2	0.0	0.1	2.6	1.3
Switzerland	Basel	13,654	0	4.3	99	0.0	3.8	0.2	0.0
	Geneva	16,775	0.5	1.1	92.6	1.1	1.7	6.2	0.8
	Grisons	2,788	0.7	0.5	91.9	0.5	2.4	6.3	0.0
	St. Gallen	16,588	0.7	1.2	92.8	0.7	0.5	4.4	0.4
	Ticino	10,784	3	0.3	91.4	0.0	0.6	6.8	1.5
	Valais	4,533	1.5	0.4	91.2	0.4	2.4	8.2	0.9
	Zurich	777	0.3	3.9	97.3	0.5	2.7	2.2	0.0
Netherlands	Amsterdam	95,439	0	0.5	95.7	0.0	0.6	4.2	0.1
	Eindhoven	27,985	0	0	95.7	0.0	0.1	4.1	0.2
	North Netherlands	58,508	0	1	94.7	0.0	0	5.3	0.2
	Twente	41,217	0	0.7	95.1	0.2	0.1	5.1	0.4
UK England	East Anglia	131,829	0.5	0.9	86.4	2.3	10.1	0.6	0.3
	Northern Yorkshire	265,499	1.1	0.4	86.8	0.2	0	3.9	0.3
	Oxford	85,848	0.8	0.4	88.8	10.4	0	0.4	0.6
	South Western	168,672	7.8	0.1	70.2	10.9	0	10.6	1.3
	Trent	109,768	7.3	0	74	9.1	0	2.4	0.9
	West Midlands	190,726	5.1	1.1	81.9	0.0	0	4.2	0.5
UK N. Ireland	Northern Ireland	69,558	1.2	0.4	83.4	0.4	0	16.7	0.7
UK Scotland	Scotland	263,710	0.9	0.1	86.4	0.0	0	5.8	0.6
UK Wales §	Wales	120,606	12.7	0	51	42.2**	0	6.3	0.9
RARECARE		**4,082,646**	**3**	**0.5**	**85.9**	**4.7**	**1.2**	**8.2**	**0.8**

NOS= Not Otherwise Specified
Topography codes NOS: C140, C260, C268, C269, C390, C398, C399, C559, C579, C639, C689, C729, C759-C765, and C767-C768
Morphology codes: 8000, 8001
n.a.: not available
§ MV status not ascertainable for all cases from Wales CR.
** Bases of diagnosis unknown to CR (known to medical doctors)

Table 3 shows the proportion of unspecified morphology cases by CRs. Fixing a cut point at 20%, 5 CRs were identified with an high proportion of unspecified morphology cases. However, none of the registries showed

clearly outlier values. Rare tumours are defined by combinations of topography and morphology codes. While the former are widely used in the analysis of CR data and can be considered as sufficiently reliable and precise, there is less experience in the precision of morphology coding across CRs.

Unspecified morphology codes are excluded from the definition of any Layer 2 entity in the RARECARE tumour list thus, coding with a more general term such as 8000/3 or 8001/3 can result in cases attributed to a Layer 1 group of entities but not to a specific Layer 2 rare entity (the RARECARE cancer list is available on the website: www.rarecare.eu). Therefore, for each registry, total incidence calculated for all Layer 1 entities combined should be higher than incidence calculated for all Layer 2 entities combined. The difference can be taken as an indicator of the proportion of poorly specified morphology codes. This analysis is reported in Table 4 (columns 4-6). Using also here a cut point of 20 percent difference, four additional registries with critical values were identified. A final analysis focused on the registry sensitivity, defined as the proportional difference in incidence obtained by the removal of each single registry from the data in analysis (Table 4 column 7). For the reasons expressed above, positive values may be due to lower data quality, indicating that the registry data tends to lower the pooled incidence estimate. These data are quite reassuring: only one registry has a value greater that 1%, and four a value greater than 0.5%. In conclusion, incidence of all the entities was calculated both with and without the nine above critical registries. The results did not change substantially, with only one entity changing from rare to not rare category.

Table 4. Quality analysis of morphological information on diagnoses

Country	Registry	% of unspecified morphology cases	Incidence Layer 1	Incidence Layer 2	Difference %	Sensitivity
Austria	Austria	10.13	463.6	375.0	19.1	0.00
Belgium	Flanders	7.34	465.7	389.4	16.4	0.62
France	Bas Rhin	3.91	420.3	392.4	6.7	0.49
	Doubs	3.24	372.7	348.5	6.5	0.09
	Haut Rhin	2.94	422.2	376.8	10.8	0.02
	Herault	1.49	395.0	376.6	4.6	0.13
	Isère	4.14	377.8	350.4	7.3	0.07
	Manche	3.37	416.3	394.5	5.2	0.16
	Somme	5.49	368.1	334.1	9.2	-0.02
	Tarn	5.86	341.2	317.9	6.8	-0.03
Germany	Saarland	7.96	606.4	528.6	12.8	1.05
Iceland	Iceland	3.47	391.5	369.1	5.7	-0.03
Ireland	Ireland	11.02	499.3	431.7	13.5	-0.92
Italy	Alto Adige	9.18	492.6	437.6	11.2	0.03
	Biella	12.51	752.6	656.1	12.8	0.08
	Ferrara	9.65	819.9	721.6	12.0	0.36
	Firenze	17.67	679.2	542.1	20.2	0.27
	Friuli V.G.	9.79	795.4	674.6	15.2	0.56
	Genoa	16.57	773.3	614.0	20.6	0.26
	Macerata	13.05	667.8	557.5	16.5	0.03
	Modena	11.77	675.7	591.5	12.5	0.42
	Napoli	17.63	279.4	212.5	23.9	0.11
	Parma	13.10	728.2	608.5	16.4	0.19
	Ragusa	24.60	434.9	321.4	26.1	0.04
	Reggio Emilia	13.80	680.1	557.8	18.0	-0.01
	Romagna	12.32	753.2	649.6	13.8	0.15
Italy	Salerno	23.65	389.8	285.1	26.9	-0.36
	Sassari	16.41	458.2	377.8	17.5	0.00
	Trento	27.82	570.7	435.5	23.7	0.02

	Umbria	12.61	662.8	541.9	18.2	-0.03
	Varese	10.81	588.6	500.9	14.9	0.00
	Veneto	13.69	679.1	568.9	16.2	0.47
Malta	Malta	12.89	305.7	255.8	16.3	-0.04
Norway	Norway	6.68	534.3	480.3	10.1	0.25
Poland	Cracow	27.17	382.8	259.8	32.1	0.13
	Kielce	21.73	317.6	231.1	27.2	-0.29
	Warsaw	19.06	360.9	269.3	25.4	-0.23
Portugal	South Portugal	7.22	361.5	313.0	13.4	-0.09
Slovenia	Slovenia	17.93	340.3	288.7	15.2	-0.04
Slovakia	Slovakia	9.61	285.4	228.2	20.0	-1.19
Spain	Basque Country	11.43	399.5	343.1	14.1	-0.10
	Girona	12.83	440.1	381.0	13.4	0.17
	Murcia	11.07	306.1	260.8	14.8	-0.12
	Navarra	7.57	559.1	511.6	8.5	0.10
	Tarragona	13.33	402.1	336.1	16.4	-0.03
Sweden	Sweden	2.62	468.2	434.3	7.3	0.24
Switzerland	Basel	0.23	439.4	428.5	2.5	0.35
	Geneva	6.18	501.3	454.3	9.4	0.00
	St. Gallen	4.39	389.4	358.4	8.0	-0.05
	Ticino	6.82	480.9	436.0	9.3	0.06
	Valais	8.23	400.1	361.5	9.6	-0.03
Netherlands	Amsterdam	4.24	406.4	377.2	7.2	1.25
	Eindhoven	4.14	393.3	361.1	8.2	-0.23
	North Netherlands	5.29	389.4	359.9	7.6	0.09
	Twente	5.06	431.4	386.4	10.4	-0.11
UK England	East Anglia	0.63	597.1	529.0	11.4	-0.04
	Northern Yorkshire	3.87	575.4	499.4	13.2	-0.63
	Oxford	0.38	376.4	319.0	15.2	-0.89
	South Western	10.58	476.0	353.1	25.8	-0.48
	Trent	2.44	426.4	327.6	23.2	-0.55
	West Midlands	4.19	424.6	345.6	18.6	-1.26
	Northern Ireland	16.68	485.3	391.4	19.3	-0.62
UK Scotland	Scotland	5.81	619.3	532.0	14.1	0.16
UK Wales	Wales	6.27	497.3	357.7	28.1	-0.13
RARECARE		**8.43**	**481.3**	**406.7**	**15.5**	

Data quality study on a sample of rare tumours

Table 5 shows quality indicators for the data on the selected group of rare cancers included in the data quality study. Data were archived from 1995 to 2002 by the 76 CRs whose data were used for the RARECARE estimates. The proportion of DCO cases was low for all the 8 tumours considered (<5%). The proportion of cases discovered at autopsy was 0.5%, higher proportion were reported for liver angiosarcoma (10 cases), malignant digestive endocrine tumours (277 cases) and mesothelioma (236 cases). A high proportion of cases (87% overall) were MV with higher proportion of "bases of diagnosis unknown" for tumours of the central nervous system and leukemia. Follow-up was complete for most tumours, with follow-up censored before five years in 1.08% of cases overall.

Table 5. Data quality indicators of malignant tumours included in the data quality study (diagnosed in all the 76 European CRs included in the analysis, cases diagnosed 1995-2002)

	No cases	DCO (%)	Autopsy (%)	Microscopic verification (%)	bases of diagnosis unknown (%)	cases 1995-1998 censored before 5-years (%)
Mesothelioma	15,516	2.12	1.52	89.05	3.17	0.19
Liver angiosarcoma	149	2.01	6.71	94.63	2.01	0.67
Sarcoma	52,090	0.61	0.43	96.25	1.90	1.32
Oral cavity tumours	30,363	1.46	0.04	94.78	3.03	1.01
CNS tumours	59,517	4.40	0.45	70.05	6.16	0.53
Gonadal germ cell tumours	25,833	0.05	0.06	98.25	1.24	2.93
Leukemia	95,298	4.47	0.38	87.11	5.80	0.91
MDET	11,658	0.24	2.38	97.41	1.48	1.39
ALL tumours	**290,424**	**2.76**	**0.48**	**87.60**	**4.16**	**1.08**

CNS= central nervous system
MDET=malignant digestive endocrine tumours

The quality indicators in the CRs participating in the data quality study were similar to those reported in Table 5 which refer to the complete RARECARE database. This is important because it confirms that CRs participating to this study adequately represent all the RARECARE CRs.

Table 6 shows the number of cases reviewed by each CR per each tumours. About 18,000 cases were reviewed by the participating CRs.

Table 6. Number of tumours reviewed by Cancer Registry

		Central Nervous System	Gonadal germ cell	Leukemia	Liver angiosarcoma	Malignant Digestive Endocrine	Mesothelioma	Oral cavity tumours	Sarcoma	Total
Austria	Austria	188	840	1568	251	829	231	333	430	4,670
Belgium	Flemish	52	249	629	32	357	266	166	283	2,004
Estonia	Estonia	38	181	0	122	0	19	38	38	442
France	Côte d'Or Digestive	-	-	-	5	86	-	-	-	91
	Côte d'Or Hemat.	-	-	33	-	-	-	-	-	33
Ireland	Ireland	127	132	639	14	244	81	66	171	1,488
Italy	Alto Adige	24	12	70	17	73	10	13	49	268
	Biella	6	2	37	11	30	15	6	11	142
	Ferrara	43	5	117	29	52	33	12	15	313
	Firenze	130	124	462	148	135	58	68	44	1,184
	Genoa	54	48	-	47	59	143	29	48	404
	Modena	78	56	112	33	7	17	5	62	348
	Napoli	24	13	91	47	7	24	12	22	245
	Parma	38	34	167	31	90	27	6	32	418
	Ragusa	23	35	73	32	19	19	8	6	231
	Reggio Emilia	69	46	134	60	35	25	22	28	419
	Romagna	-	-	-	-	155	45	-	101	301
	Trento	34	9	39	44	27	2	19	14	189
	Varese	26	12	91	23	64	30	13	38	302
	Veneto	24	35	-	83	78	38	19	50	313
Malta	Malta	15	10	51	7	37	5	9	26	178

The Netherl.	Amsterdam	77	10	257	27	218	113	17	-	719
	North Netherl.	-	-	-	9	33	35	11	94	182
	Twente	-	-	-	11	8	32	9	57	117
Poland	Kielce	230	113	249	61	32	51	29	75	796
	Warsaw	-	64	-	114	101	43	3	44	369
Slovenia	Slovenia	31	42	168	67	94	36	59	84	573
Sweden	Albacete	-	-	-	23	-	-	16	-	39
	Basque Country	-	19	-	25	-	36	-	-	82
	Castilla la Mancha	31	10	0	2	12	4	4	9	51
	Girona	28	16	106	68	19	19	15	35	334
	Navarra	14	5	52	0	20	7	1	18	121
	Tarragona	50	7	-	17	-	6	18	31	93
	Stockholm	34	11	0	18	20	33	16	28	183
Switzerland	Geneva	7	-	-	-	-	10	-	29	78
	St. Gallen	-	3	-	7	48	-	-	-	58
	Ticino	3	1	42	20	41	9	6	18	138
	Valais	2	3	19	10	14	2	3	9	70
	Total	1,500	2,147	5,206	1,515	3,044	1,524	1,051	1,999	17,986

- (tumour not revised by cancer registry)

The results of the revision by tumours reviewed in the data quality study follow.

Mesothelioma

The review focused on:

1. long term survivors (alive 2 or more years after diagnosis) with ICD-O morphology 9050-9053 (mesothelioma) of **any sites** (to verify the diagnostic accuracy and the quality of follow-up)

2. all cases with a generic diagnosis of pleural cancers (to ascertain the completeness of incidence of mesothelioma of the pleura).

Mesothelioma long survival were 12% of all mesothelioma cases in the RARECARE database and 15% of the mesothelioma cases among the CRs contributing to the study. The proportion of cases of pleural cancers different from mesothelioma was 13% in the RARECARE database and 18% among CRs contributing to the study.
Although the proportions were relatively low, the issue of follow-up and incidence completeness are relevant for a lethal and professional-related cancers such as mesothelioma.

The changes in diagnosis and follow-up resulting from the revision follow:

1. Mesothelioma long term survivors (alive > 2 years after diagnosis)

Out of the 678 cases reviewed:

- 578 (85%) were confirmed mesothelioma **long survivors**
- 69 (10%) were confirmed as mesothelioma but **not long survivors**
- 18 (3%) **were not mesothelioma** (neoplasm NOS, adenocarcinoma, sarcoma, lymphoma)
- 13 cases were deleted from the incidence series (7 not malignant, 6 administrative errors of CR)

2. Pleural cancers (not mesothelioma)

Out of the 846 cases of pleural cancers reviewed:

- **525(62%) were confirmed pleural cancers and in detail:**
  414 neoplasm, NOS
  68 mesothelioma
  43 sarcoma

- **298 (35%) were not tumours of the pleura. They were metastasis from other organs.**
  166 adenocarcinoma (thorax, breast, ovary, digestive organs, unknown primary)
  71 neoplasm, NOS (thorax, breast, digestive organs, unknown primary)
  33 lymphoma
  18 squamous cell (thorax, urinary system)
  9 sarcoma (thorax, soft tissue, unknown primary)
  1 thymoma

- **23 were not malignant tumours or CRs administrative errors**

In conclusion

- 647 cases were confirmed malignant mesothelioma (578 + 69)
- 31 cases were not mesothelioma (18+13)
- 68 new cases of mesothelioma were retrieved from pleural cancers
- 37 (68-31) cases of mesothelioma will contribute to the estimate of mesothelioma incidence and survival after the revision

The majority of mesothelioma long survivors reviewed 85% (578/647) were confirmed as mesothelioma long survivors. This suggest the good quality of diagnosis and follow-up.

In addition, only 68 cases of mesothelioma were retrieved from pleural cancers confirming a good completeness of incidence. However, common errors in topography coding are still present, thus further effort is needed to ensure standardisation of mesothelioma registration across CRs.

Considering the high lethality of the mesothelioma it would be interesting to further study the 578 cases confirmed long term survivors after the revision (A centralised revision of pathological reports and samples could be considered).

Liver angiosarcoma

The review focused on:

1. 1,477 liver cancers with a morphologic code **different from** the most frequent primary liver cancers: cholangiocarcinoma, hepatocellular carcinoma, hepatoblastoma and cystadenocarcinoma (to ascertain the completeness of incidence of liver angiosarcoma)

2. 19 sarcoma NOS of the liver (to ascertain the quality of diagnosis and completeness of incidence)

3. 19 angiosarcoma long survivors (>1yr) (to verify quality of follow-up and quality of diagnosis)

Liver angiosarcoma is a very rare tumour. Out of all sarcomas of the digestive tract, only 4% of cases wee liver angiosarcoma in the RARECARE database. Among the CRs participating to the data quality study, the proportion of liver angiosarcoma was 5%.
Liver angiosarcoma is a lethal tumour thus the proportion of liver angiosarcoma long survivors (>1 year) should be very low. Liver angiosarcoma long survivors were 15% of all liver angiosarcoma cases in the RARECARE database and 23% of all liver angiosarcoma cases across CRs included in the data quality study.

The changes in diagnosis and follow-up resulting from the revision follow:

1. Liver cancers morphologies different from the frequent liver cancers

After the revision of 1,477 cases:

- **1,242 (84%) were confirmed liver neoplasm and in details:**
  424 adenocarcinoma
  370 other epithelial neoplasm
  233 neoplasm, NOS
  121 hepatocellular carcinoma
  22 cholangiocarcinoma
  10 lymphoma
  6 liver angiosarcoma (no new cases)
  3 hepatocholangiocarcinoma
  49 neuroendocrine tumours
  4 sarcoma
- **235 were liver metastasis:**
  60 organs of the digestive tract
  52 organs NOT of the digestive tract
  116 unknown primary site
  7 deleted from the incidence series (no cancer cases)

2. Sarcoma NOS of the liver

Only 9 CRs had cases of sarcoma NOS of the liver thus 19 cases were reviewed. Out of these, 2 liver angiosarcoma were retrieved (Table 7).

Table 7. Morphology after the revision of sarcoma NOS of the liver

Morphology	**Freq.**	**Percent**
sarcoma, NOS	7	36.8
Embryonal sarcoma	1	5.3
hepatocellular carcinoma	6	31.6
GIST	2	10.5
neoplasm, NOS	1	5.3
liver angiosarcoma	**2**	**10.5**
Total	**19**	**100**

3. Angiosarcoma long survivors (>1yr)

Due to the exceptional occurrence of liver angiosarcoma only 6 out of the 22 European CRs had cases of liver angiosarcoma long survivors.

Out of the 19 liver angiosarcoma long survivors 7 were confirmed real long survivors (survival range from 15 months to 13 years). Twelve were NOT long survivors (for 7 the date of dead was changed, the other 5 were lost to follow-up).

In conclusion

- Only 2 cases of liver angiosarcoma were retrieved from the revision of sarcoma NOS
- 7 out of 19 cases were confirmed angiosarcoma long term survivors

In addition, the revision retrieved new 121 hepatocellular carcinoma and 22 cholangiocarcinoma and identified 235 cases which were liver metastasis.

Liver angiosarcoma is a lethal tumour and it is associated with a specific occupational exposure thus it will be important to ensure that all cases will be always properly identified/diagnosed. A centralised system of pathologic review could be envisioned for liver angiosarcoma in order to support pathologist in making diagnosis.

A general comment is that the morphology codification of liver cancers should improve to ensure a complete identification of typical liver cancers (hepatocellular carcinoma, cholangiocarcinoma) and to distinguish liver cancers from cases of liver metastasis.

Sarcoma

The review focused on:

- sarcoma NOS (8800) and the descriptive ICD-O3 morphology codes 8801-8806 of any sites (to verify the quality of diagnosis)

Out of all sarcoma of any sites, sarcoma NOS were 14% in the RARECARE database and 12% across CR participating to the data quality study.

About 2,000 cases of sarcoma NOS were reviewed. Out of those, 79% were confirmed sarcoma NOS and 12% had a better definition of the sarcoma morphology. One hundred nineteen (119) Gastro Intestinal Stromal Tumours (GIST) were retrieved mainly from the year 2000 onward (Figure 1). The remaining few cases (No=49) were not sarcomas.

Figure 1. GIST by cohort of diagnosis

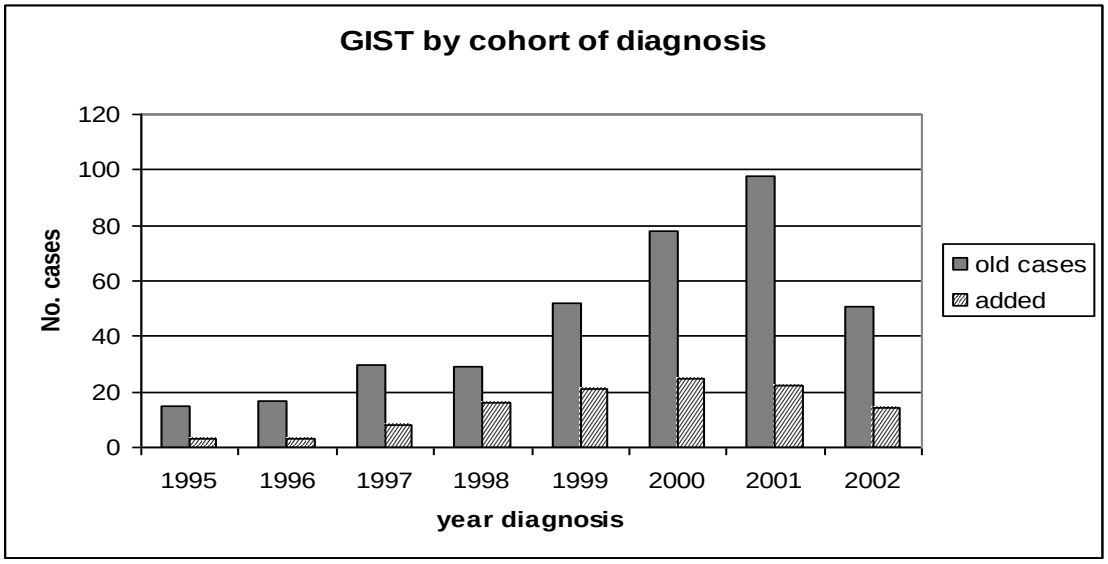
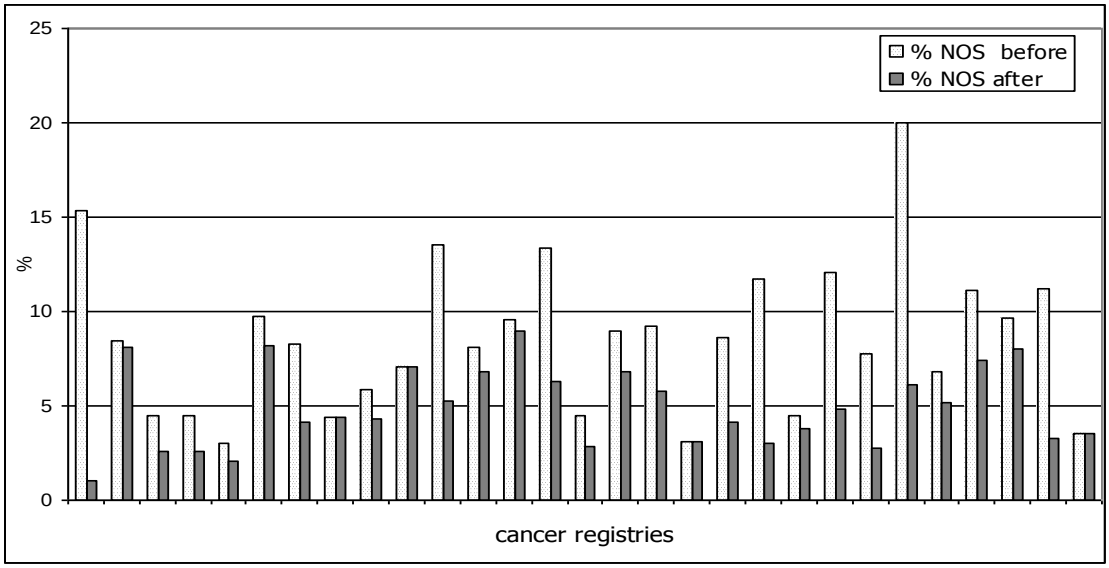


Figure 2 shows % of sarcoma NOS by CR before and after the revision. The variability of sarcoma NOS across CRs was still present after the revision however the proportion of sarcoma NOS decreased in all CRs especially in those with high proportion of unspecified morphology before the revision.

Figure 2. Sarcoma NOS before and after the revision by CRs



In conclusion

- the majority of cases didn't change the diagnosis and were confirmed as sarcoma NOS
- 119 cases of GIST were identified among sarcomas NOS.

The revision confirms the difficulties in making a specific diagnosis for sarcoma and therefore the relatively high percentage of sarcoma NOS reported by CRs. Nevertheless, the revision allowed CRs to reduce the number of sarcoma NOS registered supporting the idea that more attention should be focused at CR level in registering sarcomas. It is worth stressing that it is possible to have a diagnosis of sarcoma NOS, since also expert pathologists may give this diagnosis.

The identification of GIST especially from the year 2000 was expected considering that this new morphology was introduced with the ICD-O3.

Tumours of the oral cavity

The review focused on:

1. Carcinoma NOS (morphology codes 8000, 8001, 8010, 8011) of the oral cavity (ICD-O site codes C02.0-02.3, 02.9, 03.0-05.0, 06.0-06.9) to assess the quality of diagnosis.

2. Unspecific site codes such as the "overlapping lesion of tongue" (C02.8) and "Palate NOS" (C05.9) to distinguish between oral cavity and oropharynx, two separate cancer site in our list of tumours entities.

The proportion of carcinoma NOS of the oral cavity was very low being 6% in the RARECARE database and 5% across CRs included in the data quality study.
The proportion of cases of unspecified sites of oropharynx among all cancers of the oropharynx was very low: 6% in the RARECARE database and 5% across CRs participating to the data quality study.

The changes in morphology and subsite specification resulting from the revision follow:

1. Carcinoma NOS

Out of the 626 cases of carcinoma NOS reviewed, 89% were confirmed carcinoma NOS. Only 53 cases of squamous cell carcinoma were retrieved (Table 8).

Table 8. New morphology after the revision of the carcinoma NOS of the oral cavity

Morphology	**Freq.**	**Percent**
carcinoma NOS	556	88.8
squamous cell ca	53	8.5
adenocarcinoma	5	0.8
other epithelial neoplasms	1	0.2
benign or borderline tumour	11	1.8
Total	**626**	**100**

2. Unspecific site codes

Out of the 459 cases reviewed, 72% were confirmed as belonging to an unspecified site. Thirty-nine cases were identified as oropharynx and 73 as belonging to the oral cavity (Table 9).

Table 9. New topography after the revision of unspecified sites oropharynx

Topography	**Freq.**	**Percent**
unspecified sites oropharynx	331	72.1
oropharynx	39	8.5
oral cavity	73	15.9
palate, overlapping lesion	4	0.9
tonsil	7	1.5
nasopharynx	1	0.2
hypopharynx	1	0.2
skin	1	0.2
not neoplasm	2	0.4
Total	**459**	**100**

In conclusion

- 89% of carcinoma NOS were confirmed as non otherwise specified (NOS) and
- almost all the cases with a new pathological diagnosis were squamous cell carcinoma
- 73 new cases belonging to the oral cavity were identified.

The revision confirms the good quality of diagnosis (with regard to the morphology specification) for the tumours of the oral cavity however, it supports the idea that the topography can and should be ameliorated considering the different prognosis between oral cavity tumours and those of the oropharynx (5-year survival: oropharynx = 37%; oral cavity=59% - RARECARE).

The prognosis of head and neck cancers varies considerably according to the precise anatomical site of origin of the tumours, which affects the early appearance of symptoms and, therefore, the stage at diagnosis and the possibility of radical surgery [5,6].
Site and subsite are important determinants of prognosis and differences in subsite distribution across European population explain a considerable part of the survival differences across EU. It is essential that CRs take steps to ensure that subsite information is accurate and complete [5,6].

Tumours of the Central Nervous System

The review focused on:

1. Long-term survivors (> 1 year) of the brain (C71) with a diagnosis of unspecified morphology codes (8000, 8001, 8010) to verify both the quality of diagnosis and follow-up.

2. Cases with diagnosis of Glioma NOS (9380) to verify the quality of diagnosis of brain tumours characterized by the availability of effective treatment (selected gliomas, germ-cell tumours, lymphomas).

The proportion of long-term survivors of the brain with a diagnosis of unspecified morphology on all cancers of the brain was low: 4% in the RARECARE database and 5% across CRs participating to the data quality study. Also the proportion of glioma NOS out of all brain tumours is low however, it was slightly higher (9%) in the RARECARE database than in the sample of CRs participating to the data quality study (6%).

The changes in follow-up and diagnosis resulting from the revision follow:

1. Long-term survivors

Out of the 919 cases reviewed:

- **681 (74%) were confirmed brain tumours long survivors**
- 119 (13%) were brain tumours NOT long survivors
- 46 were NOT brain tumours (metastasis)
- 73 were not malignant tumours (50 of the brain)

2. Glioma NOS

After the revision of 581 cases, 79% were confirmed glioma NOS; for 117 the pathological diagnosis improved (97 astrocytic, 5 oligodendrglial, 2 ependimal and 3 non glial/embryonal) (Table 10). These latter will contribute to the incidence of second layer entities of the glial tumours of CNS astrocytic tumours.

Table 10. New morphology after the revision of glioma, NOS

Morphology	**Freq.**	**Percent**
glioma malignant	458	78.8
astrocytic tumours	**97**	**16.7**
oligodendrglial	**5**	**0.9**
non glial/embryonal tumour	**3**	**0.5**
ependimal tumours	**2**	**0.3**
sarcoma	2	0.3
not brain tumour (leukemia)	1	0.2
neoplasms, NOS	4	0.7
not malignant	9	1.6
Total	**581**	**100**

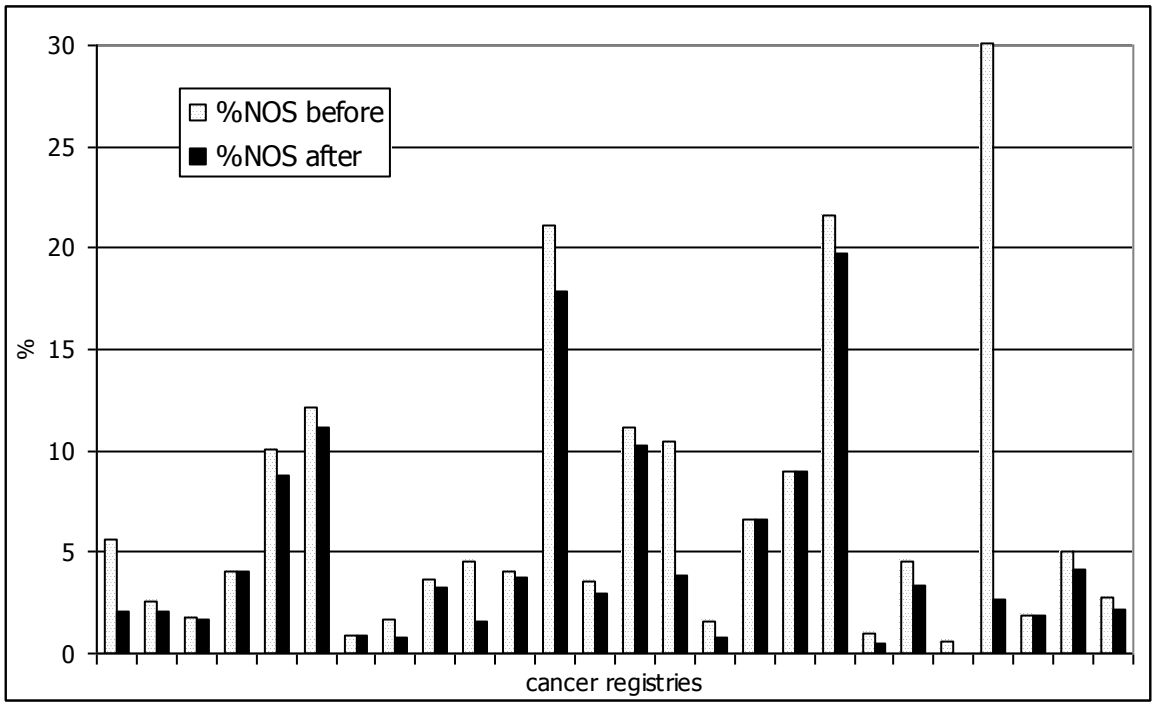
In conclusion

- 681 (74%) were confirmed brain tumours long survivors
- 165 (119 + 46) were either brain tumours NOT long survivors (mainly lost to follow-up) or NOT brain tumours
- 73 were benign tumours (72 reported as brain long survivors before the revision)

The revision even confirming the majority of long-term survivors, shows problems related to the goodness of diagnosis or difficulties in the collection of more detailed information. Figure 3 reports percentage of long-term survivors of the brain with unspecified morphology by CR before and after the revision. The proportion

of NOS decreased in all CRs and especially in those with high % of unspecified morphology before the revision.

Figure 3. Proportion of long term survivors of the brain tumours with unspecified morphology before and after the revision by CRs



The quality of diagnosis seems good considering the difficulties related to make diagnosis in such an inaccessible organ like brain. However, common errors in morphology coding (such as epithelial tumours in the brain) are still present, further effort is needed to ensure standardisation of cancer registration across CRs.

Germ cell tumours

The review focused on:

1. morphology NOS (8000-8010) cases of the testis (C62, C63.0, C63.1) and of the ovary (C56).

The proportion of unspecified morphology cases of the testis was very low: 3% in the RARECARE database and 4% across CRs participating to the study. The proportion of unspecified morphology was higher in the ovary: 18% in the RARECARE database and 21% across CR of the data quality study. However, the study reviewed only the morphology NOS microscopically verified which account for 6% of cases in the RARECARE database and 7% of cases across CR of the data quality study.

Out of the 2,147 cases of morphology NOS of ovary and testis:

- **1,973 (92%) were confirmed morphology NOS**
  - 1962 (91%) morphology NOS testis and ovary
  - 11 morphology NOS (other sites)
- 106 adenocarcinoma (103 adenocarcinoma of the ovary + 3 adenocarcinoma which were metastasis from other organs: 2 to the ovary and 1 to the testis from breast, stomach and prostate respectively)
- **20 germ cell (4 ovary, 16 testis)**
- **12 sex cord tumours (ovary)**
- **9 malignant immature teratomas**
- 3 squamous cell carcinoma
- 3 mullerian mixed tumours (ovary)
- 3 sarcoma
- **1 trophoblastic tumours of testis**
- 4 others (1 transitional, 1 mesothelioma, 1 lymphoma, 1 carcinoid)
- 13 not malignant

The proportion of cases with unspecified pathological diagnosis of gonads was already low before the revision (lower in testis than ovary). Also the variability among registries was low.

The 20 cases of germ cell tumours retrieved will have a negligible impact on the incidence of these tumours. However, it is important to ensure the appropriate diagnosis of these tumours considering their good prognosis due to the availability of specific treatment for germ cell tumours.

Leukemia

The review focused on:

1. All the leukaemia, NOS (9800, 9801, 9820, 9860) and
2. Chronic myeloid leukaemia (CML), NOS (ICD-O3 9863) to assess the quality of diagnosis.

The proportion of leukemia NOS out of all cases of leukemia in the RARECARE database was 7.4% and it was slightly higher across CRs participating to the data quality study (9%). The proportion of CML, NOS was 11% in the RARECARE database and 12% across CRs of the data quality study.

The changes in morphology codes after the revision follow.

1. Leukemia, NOS

Out of 2,253 cases revised, 88% were confirmed leukemia, NOS. Table 11 shows the detailed results of the revision.

Table 11. Morphology after the revision of the leukemia, NOS

Morphology	**Freq.**	**Percent**
leukemia NOS	1,972	87.5
acute myeloid leukemia	101	4.6
lymphoid diseases	82	3.6
myelodisplastic syndrome	26	1.1
myeloproliferative neoplasms	24	1.1
myelodisplastic/myeloproliferative diseases	22	1.0
CML typical	3	0.1
CML atypical	2	0.1
neoplasms NOS	1	0.04
adenocarcinoma	1	0.04
deleted from the incidence series	16	0.7
not malignant	3	0.1
Total	**2,253**	**100**

2. CML, NOS

Out of the 2,953 cases, 87% were confirmed CML, NOS. However, 239 cases of CML, typical and 29 cases of CML, atypical were retrieved (Table 12).

Table 12. Morphology after the revision of the CML, NOS cases

Morphology	**Freq.**	**Percent**
CML, NOS	2,556	86.6
CML, typical	239	8.1
CML, atypical	29	1.0
lymphoid diseases	16	0.5
leukemia, NOS	2	0.1
acute myeloid leukemia	30	1.0
myelodisplastic/myeloproliferative diseases	42	1.4
myeloproliferative neoplasms	22	0.8
myelodisplastic syndrome	12	0.4
deleted from the incidence series	4	0.1
not malignant	1	0.03
Total	**2,953**	**100**

In conclusion

- The majority of morphology NOS were confirmed: among all leukaemia, leukaemia NOS decreased from 9% to 8% after the revision.

- Overall 242 cases of typical CML and 31 cases of atypical CML were retrieved. The proportion of CML NOS among all the leukaemia became 10%, with low variability across registries.

Even if the overall quality of data seems good, the proportion of leukemia NOS was a bit too high in few CRs. Because treatment is available for typical CML, further effort should be put in place by CRs to reduce the number of CML and leukemia NOS registered and to identify CML typical and atypical.

Malignant digestive endocrine tumours (MDET)

The review focused on:

1. undifferentiated (8020/3) and anaplastic (8021/3) carcinomas of the digestive tract (C15 to C25) to find small cell MDET and assess diagnostic accuracy. Among endocrine tumours, small cell MDET are low prognosis neoplasms.

2. all carcinoids (8240-8244) of the digestive tract (C15 to C25) to verify the behaviour. A high number of carcinoids of digestive tract are not malignant. Criteria used in this study for defining the behaviour of carcinoids were the local invasion and the dimension of the tumour (see protocol).

The proportion of small cell MDET of the digestive tract was low: 9% in the RARECARE database and 8% across CRs of the data quality study with differences in the proportion of small-cell MDET across CRs: from 3% to 30%.
Lepage and colleagues reported a proportion of small cell MDET of 22% in the dataset of their analysis. They excluded from the analysis 11 CRs unable to distinguish between well-differentiated and small-cell MDET. Even among CRs included in their analysis, they found a considerable variation in the proportion of small-cell MDET according to the geographic regions: from 3.4% in Northern Europe to 30.3% in the United Kingdom [7].

The proportion of carcinoids of the digestive tract out of all the MDET of the digestive tract was around 65% in both, the RARECARE database and in the sample of CR included in the data quality study. Out of all the MDET of the digestive tract, those of the appendix were 13% in the RARECARE database and 18% across CRs of the data quality study. Appendix MDET are usually benign, surprisingly high incidence and survival rates could be related to high proportion of MDET of the appendix and should be carefully revised.

The results of the revision follow:

1. Undifferentiated and anaplastic carcinoma of digestive tract

Out of the 929 cases reviewed only 10 small cell carcinoma were retrieved (Table 10).

Table 10. Morphology after the revision of carcinoma, NOS of the digestive tract

Morphology	**Freq.**	**Percent**
undifferentiated carcinoma	825	88.79
adenocarcinoma	68	7.32
small cell endocrine carcinoma	**10**	**1.08**
other epithelial neoplasms, NOS	9	0.97
neuroendocrine carcinoma	7	0.75
squamous cell carcinoma	5	0.54
cloacogenic carcinoma	1	0.11
GIST	1	0.11
lymphoma	1	0.11
deleted from incidence series	2	0.22
Total	**929**	**100**

2. Carcinoids of the digestive tract

Information on local invasion and dimension of the tumour were available, in the pathological report, only for 353 out of the 2,115 cases reviewed. Thus, the results refer only to the 353 cases with information available to define the behaviour (Table 11).

Table 11. Behaviour after the revision of carcinoids of the digestive tract

Behaviour	**/3**	**/1**	**cases deleted from incidence**	**Total**
stomach	31	18	0	49
small intestine	146	25	1	172
colon	36	2	2	40
recto sigmoid junction	2	1	0	3
rectum	12	16	0	28
anus and anal canal	1	1	0	2
gall bladder	1	0	0	1
other parts of biliary tract	3	2	0	5
pancreas	17	7	3	27
appendix	7	19	0	26
Total	**256**	**91**	**6**	**353**

/1=borderline; /3=malignant

After the revision, the majority of carcinoids of the appendix changed the behaviour from malignant to border line. The benign behaviour of carcinoids of the appendix is well known and previous studies (Lepage et al, 2009) have already stressed the impact that this issue might have on survival. CRs have to pay special attention in assigning the behaviour of such tumours. Additional criteria should be agreed on and used to properly classify the behaviour of carcinoids.

Impact of the revision on incidence and survival

Mesothelioma

The revision had a negligible impact on incidence (Table 12) of mesothelioma however it had an interesting impact on survival (Table 13).

Table 12. Malignant mesothelioma crude incidence rate before and after the revision

		No cases	incidence rate	Lower 95%CI	Upper 95%CI
before revision	**MALIGNANT MESOTHELIOMA**	**4,229**	**1.4**	**1.4**	**1.5**
	Mesothelioma of the pleura and pericardium	3,764	1.3	1.2	1.3
	Mesothelioma of the peritoneum tunica vaginalis	355	0.1	0.1	0.1
after revision	**MALIGNANT MESOTHELIOMA**	**4,268**	**1.5**	**1.4**	**1.5**
	Mesothelioma of the pleura and pericardium	3,807	1.3	1.3	1.3
	Mesothelioma of the peritoneum tunica vaginalis	352	0	0.1	0.1

Table 13. Malignant mesothelioma 1 and 5-year relative survival before and after the revision

		1 year				5-year			
		No of cases	relative survival %	Lower 95% CI	Upper 95% CI	No of cases	relative survival %	Lower 95% CI	Upper 95% CI
before revision	**MALIGNANT MESOTHELIOMA**	**2,702**	**39.5**	**37.6**	**41.4**	**2702**	**7.2**	**6.2**	**8.4**
	Mesothelioma of the pleura and pericardium	2,421	40.2	38.1	42.2	2421	6.1	5.1	7.3
	Mesothelioma of the peritoneum tunica vaginalis	225	31.6	25.5	37.9	225	13.9	9.4	19.3
after revision	**MALIGNANT MESOTHELIOMA**	**2,715**	**37.7**	**35.9**	**39.6**	**2715**	**5.5**	**4.6**	**6. 6**
	Mesothelioma of the pleura and pericardium	2,441	38.4	36.4	40.4	2441	4.6	3.7	5.5
	Mesothelioma of the peritoneum tunica vaginalis	221	29.4	23.41	35.6	221	12.6	8.3	17.9

Even if 85% were confirmed mesothelioma long survivors, 5-year survival in the sample of CRs studied, decreased from 7.2% before the revision to 5.5% after the revision. Inferring/expanding the results of the revision to the entire database of RARECARE is possible to understand what kind of impact a correction of misclassified cases would have on the mesothelioma survival estimates. We assume 2 scenarios:

(A): all misclassified cases are in the subset of 678 cases revised only
(B): the proportion of misclassification among all the cases of the RARECARE database is the same of that found in the revised subset

Five years survival before the revision and after the revision according to the 2 scenarios follow:

	5-year survival (%) before revision	5-year survival (%) after revision	
		misclassification only in the CR of the study	misclassification in all the CR of the study
MALIGNANT MESOTHELIOMA	**5.5**	**5.0**	**4.2**
Mesothelioma of the pleura and pericardium	4.9	4.4	3.6
Mesothelioma of the peritoneum tunica vaginalis	11.4	10.9	10.4

In both cases the 5-year survival decreased. The impact is higher for scenario (B) which describes a situation more similar to the true one.

Liver angiosarcoma

The impact of the revision on the incidence was not estimated considering that only 2 cases of liver angiosarcoma were retrieved from the revision.

The impact on survival is more interesting. The number of cases considered is low (19) and only few CRs reported liver angiosarcoma long-term survivors with a proportion of cases different across CR. This is due to the fact that liver angiosarcoma is a very rare and lethal tumour.

Five years survival decreased from 23% before the revision to 19% after the revision (Table 14). This was due to the fact that after the revision only 7 out 19 were confirmed liver angiosarcoma long-survivors. The number of long-term survivors decreased mainly in CRs reporting higher number before the revision confirming that liver angiosarcoma long-survivors are exceptional cases.

Table 14. 1 and 5-year relative survival of liver angiosarcoma before and after the revision

	Relative Survival (%) before revision	Relative Survival (%) after revision
1-year	30.9	21.0
5-year	23.5	19.1

Sarcoma

The revision, as envisioned, increased the number of Gastro Intestinal Stromal Sarcoma (GIST) since this is a new morphology of the ICD-O3. The revision had a negligible impact on the incidence since only 100 new cases were retrieved (Table 15).
The 5-year survival decreased from 72% before the revision to 68% after the revision (Table 16). This is most likely to be due to the fact that cases retrieved from 1995 were old cases with a poorer prognosis due to the time period they were diagnoses characterised by limited access to treatment, poorer knowledge of the specific disease, difficulties in making diagnosis.

Table 15. GIST crude incidence rate before and after the revision

	No of cases	Incidence rate	Lower 95% CI	Upper 95% CI
Before revision	371	0.15	0.13	0.16
After revision	483	0.19	0.17	0.2

Table 16. GIST 1 and 5-year relative survival before and after the revision

	1 year relative survival				**5-year relative survival**			
	No of cases	Relative survival %	Lower 95% CI	Upper 95% CI	No of cases	Relative survival %	Lower 95% CI	Upper 95% CI
Before revision	143	86.2	78.6	91.2	143	72.4	61.9	80.6
After revision	194	84.6	78.2	89.3	194	67.6	59.0	75.0

Oral Cavity

The impact of the revision was negligible on both, incidence (Table 17) and survival (Table 18). The proportion of carcinoma NOS of oral cavity was low (6%) among CR participating to the study. The revision retrieved mainly cases of squamous cell carcinoma, the most common morphology of this site.

Also the proportion of unspecified sites of oropharynx was low among CRs participating to the study: 6%. After the revision, 39 cases were identified as belonging to the oropharynx and 73 to the oral cavity out of the 459 cases with unspecified topography revised. This limited number of cases justifies the negligible impact on incidence and survival however and more important it demonstrates that subsite can be better identified.

As already stressed, because of the prognostic value of subsite for head and neck cancers, CRs have to work to ensure a complete and adequate identification of site and subsite.

Table 17. Crude incidence rate of tumours of oropharynx and oral cavity before and after the revision

	Incidence rate before revision	Incidence rate after revision
EPITHELIAL TUM OF THE OROPHARYNX	**2.98**	**2.96**
Squamous cell carcinoma and variants of the Oropharynx	2.77	2.75
EPITHELIAL TUM OF THE ORAL CAVITY AND LIP	**4.67**	**4.69**
Squamous cell carcinoma and variants of the Oral cavity	**3.12**	**3.16**
Squamous cell carcinoma and variants of the Lip	1.2	1.2

Table 18. 1 and 5-year relative survival tumours of oropharynx and oral cavity before and after the revision

	Relative Survival (%) before revision		Relative Survival (%) after revision	
	1 year	5-year	1 year	5-year
EPITHELIAL TUM OF THE OROPHARYNX	70.1	38.0	70.1	37.9
Squamous cell carcinoma and variants of the Oropharynx	71.0	38.3	71.0	38.2
EPITHELIAL TUM OF THE ORAL CAVITY AND LIP	82.4	60.6	82.4	60.5
Squamous cell carcinoma and variants of the Oral cavity	76.9	48.5	77.0	48.6
Squamous cell carcinoma and variants of the Lip	98.5	93.2	98.5	93.2

Tumours of the Central Nervous System

The impact of the revision was negligible on both, incidence (Table 19) and survival (Table 20). The proportion of CNS long-term survivors with unspecified morphology was low (5%) among CR participating to the study thus, out of the 919 cases reviewed only 60 new cases of brain long term survivors were retrieved. However, out of the 919 long survivors reviewed, 25% of cases were either not long survivors or not brain or not malignant tumours. CRs should work to better define brain cancers.

Table 19. Crude incidence rate of CNS tumours before and after the revision

	Incidence rate before revision	Incidence rate after revision
GLIAL TUMOURS OF THE CNS AND PINEAL GLAND	**5.01**	**5.03**
Astrocytic tumours of the CNS	4.54	4.55
Oligodendroglial tumours of the CNS	0.29	0.29
Ependymal tumours of the CNS	0.19	0.19
NON GLIAL TUMOURS OF THE CNS AND PINEAL GLAND	**0.24**	**0.24**
Embryonal tumours of the CNS	0.24	0.24
Choroid plexus carcinoma of the CNS	0.01	0.01

Table 20. 1 and 5-year survival of CNS tumours before and after the revision

	Relative Survival (%) before revision		Relative Survival (%) after revision	
	1 year	5-year	1 year	5-year
GLIAL TUMOURS OF THE CNS AND PINEAL GLAND	**44.3**	**19.9**	**44.5**	**19.9**
Astrocytic tumours of the CNS	40.5	15.9	40.7	16.0
Oligodendroglial tumours of the CNS	80.5	51.8	80.9	51.7
Ependymal tumours of the CNS	84.3	66.4	84.1	66.0
NON GLIAL TUMOURS OF THE CNS AND PINEAL GLAND	**80.4**	**57.4**	**80.5**	**57.5**
Embryonal tumours of the CNS	80.3	57.1	80.4	57.2
Choroid plexus carcinoma of the CNS	86.0	72.4	86.0	72.4

Germ cell tumours

The impact of the revision was negligible on both, incidence (Table 21) and survival (Table 22). The proportion of unspecified morphologies, among CRs of the data quality study, was low and it was lower for the testis (4%) than for the ovary (21%) and, infact, the revision changed diagnosis mainly for tumours of the ovary. The revision retrieved mainly adenocarcinoma of the ovary (No=100) and only few cases of germ cell tumours. Even if all the morphology NOS would have changed the diagnosis, the impact on incidence and survival would have been negligible anyway. This because of the low proportion of morphology NOS in the complete database.

Table 21. Crude incidence rates per 100,000 person of germ cell tumours of ovary and testis before and after the revision

	Incidence rate before revision	Incidence rate after revision
EPITHELIAL TUMOURS OF THE OVARY AND FALLOPIAN TUBE	9.0	9.0
Adenocarcinoma and variants of the Ovary	5.6	5.6
Mucinous adenocarcinoma of the Ovary	0.7	0.7
Clear cell adenocarcinoma of the Ovary	0.3	0.3
Adenocarcinoma and variants of the Fallopian tube	0.3	0.3
NON EPITHELIAL TUMOURS OF THE OVARY	0.4	0.4
Mixed epithelial mesenchymal tumours of the Ovary	0.1	0.1
Sex cord tumours of the Ovary	0.1	0.1
Malignant Immature Teratomas of the Ovary	0.1	0.1
Germ cell tumours of the Ovary	0.1	0.1
TUMOURS OF THE TESTIS AND PARATESTIS	3.0	3.0
Adenocarcinoma and variants of the paratestis	0.0	0.0
Malignant Immature Teratomas of the Testis	0.6	0.6
Germ cell tumours Seminomatous of the Testis	1.7	1.7
Germ cell tumours non Seminomatous of the Testis	0.4	0.4
Trophoblastic tumours of the Testis	0.0	0.0
Sex Cord tumours of the Testis	0.0	0.0

Table 22. 1 and 5-year relative survival of germ cell tumours of ovary and testis before and after the revision

	Relative Survival (%) before revision		Relative Survival (%) after revision	
	1 year	5-year	1 year	5-year
EPITHELIAL TUMOURS OF THE OVARY AND FALLOPIAN TUBE	70.7	41.5	70.7	41.5
Adenocarcinoma and variants of the Ovary	76.2	41.6	76.1	41.5
Mucinous adenocarcinoma of the Ovary	78.6	62.1	78.5	61.9
Clear cell adenocarcinoma of the Ovary	81.2	55.7	81.3	55.5
Adenocarcinoma and variants of the Fallopian tube	81.0	47.1	81.0	47.1
NON EPITHELIAL TUMOURS OF THE OVARY	79.9	69.8	80.1	69.7
Mixed epithelial mesenchymal tumours of the Ovary	50.1	24.9	50.4	25.4
Sex cord tumours of the Ovary	91.5	85.5	91.3	83.8
Malignant Immature Teratomas of the Ovary	90.3	85.7	90.4	85.9
Germ cell tumours of the Ovary	87.9	80.5	88.0	80.6
TUMOURS OF THE TESTIS AND PARATESTIS	97.0	94.6	96.9	94.5
Adenocarcinoma and variants of the paratestis	52.8	+	52.8	+
Malignant Immature Teratomas of the Testis	96.6	93.2	96.7	93.2
Germ cell tumours Seminomatous of the Testis	98.8	97.6	98.8	97.6
Germ cell tumours non Seminomatous of the Testis	96.0	92.3	95.9	92.3
Trophoblastic tumours of the Testis	82.7	65.7	83.1	66.5
Sex Cord tumours of the Testis	98.3	91.1	98.3	91.1

+ Statistic could not be calculated

Leukemia

The revision had an interesting impact mainly on the estimates of the atypical chronic myeloid leukemia (Tables 23-24). The incidence reached 0.02/100,000 and the 5-year survival was estimated to 25%. Before the revision, the limited number of cases didn't allow an adequate estimate of both, incidence and 5-year survival.
Atypical chronic myeloid leukemia is different from the most common Typical chronic myeloid leukemia and there is general agreement that patients with Ph negative, bcr/abl negative CML have a severe clinical course that is not affected significantly by current treatment options [8].
Cases retrieved are old patients and therefore characterised by a poorer prognosis because less affected by more recent treatment discoveries.
Because of the different prognosis CRs have to work to better differentiate Atypical and Typical chronic myeloid leukemia.

Table 23. Crude incidence rate of myeloproliferative and myelodisplastic/myeloproliferative diseases before and after the revision

	Incidence rate before revision	Incidence rate after revision
MYELOPROLIFERATIVE NEOPLASMS	**2.33**	**2.28**
Chronic myeloid leukemia	1.32	1.26
Myelosclerosis with myeloid metaplasia	0.11	0.11
Essential thrombocythemia	0.26	0.27
Polycythemia vera	0.32	0.32
Mast cell tumours	0.02	0.02
Myeloproliferative diseases other	0.29	0.3
MYELODISPLASTIC MYELOPROLIFERAT DISEASES	**0.19**	**0.23**
Chronic myelomonocytic leukemia NOS	0.18	0.21
Juvenile myelomonocytic leukemia	0.00	0
Atypical chronic myeloid leukemia BCRABL negative	**0.00**	**0.02**

Table 24. 1 and 5-year relative survival of myeloproliferative and myelodisplastic/myeloproliferative diseases before and after the revision

	Relative Survival (%) before revision			Relative Survival (%) after revision		
	N	1 year	5-year	N	1 year	5-year
MYELOPROLIFERATIVE NEOPLASMS	3,067	78.16	53.7	3,002	78.7	54.2
Chronic myeloid leukemia	1,837	71.56	38.0	1,758	72.1	38.3
Myelosclerosis with myeloid metaplasia	151	80.86	44.5	153	80.5	43.9
Essential thrombocythemia	352	92.51	87.8	357	92.7	87.5
Polycythemia vera	362	93.11	87.8	364	93.2	87.7
Mast cell tumours	24	84.29	78.3	24	84.3	78.3
Myeloproliferative diseases other	341	81.36	67.7	346	81.7	67.0
MYELODISPLASTIC MYELOPROLIFERAT DISEASES	245	64.17	27.8	298	62.8	26.2
Chronic myelomonocytic leukemia NOS	243	63.85	27.0	277	62.3	25.9
Juvenile myelomonocytic leukemia	1	100.03	+	1	100.0	+
Atypical chronic myeloid leukemia BCRABL negative	1	101.3	+	20	67.7	24.9

+ statistic could not be calculated

Malignant Digestive Endocrine Tumours (MDET)

The revision had a negligible impact on both, incidence (Table 25) and survival (Table 26).

The presence of small-cell dramatically reduces survival: 5-year survival varied from 6.3% (Eastern Europe) to 11.3% (Western Continental Europe) whereas corresponding rates for well-differentiated MDET varied from 48.0% (Eastern Europe) to 62.5% (Northern Europe) [7].
CRs have problems to distinguish small cell MDET and MDET: also after checking the pathological report, the revision retrieved only 10 cases of small cell MDET. Because the presence of small-cell tumours is a major prognostic factors actions have to be taken by CRs to ensure a complete and adequate identification of such tumours. However, the limited impact of the revision of pathological review available at CRs suggests also a possible problem of diagnostic accuracy that should be better addressed by oncologists and pathologists.

Information to define the behaviour of carcinoids was available only for a limited number of cases: 353 out of the 2,115 revised. Out of the 353, 25% were actually benign tumours confirming problems to code the behaviour for carcinoids especially for those of the appendix. The revision had a negligible impact. A data set with complete information at least on tumour size and local invasion would give more evidence on the importance of the impact of high proportion of appendix carcinoids on incidence and survival of MDET.

Table 25. Incidence crude rate of MDET before and after the revision

	Incidence rate before revision	Incidence rate after revision
NEURO ENDOCRINE TUMOURS	2.63	2.60
Well diff endocrine tumours, carcinoid	0.37	0.37
Well diff endocrine tumours, atypical carcinoid	0.00	0.00
Poorly diff endocrine carcinoma lung small cell excluded	**0.56**	**0.56**
Mixed endocrine exocrine carcinoma	0.00	0.00
Endocrine carcinoma of Thyroid gland	0.29	0.29
Well diff endocrine carcinoma not functioning of Digestive organs	**1.24**	**1.20**
Well diff endocrine carcinoma functioning Pancreas Digest tract	0.02	0.02
Endocrine carcinoma of Skin	0.14	0.14

Table 26. 1 and 5-year relative survival of MDET before and after the revision

	Relative Survival (%) before revision		Relative Survival (%) after revision	
	1 year	5-year	1 year	5-year
NEURO ENDOCRINE TUMOURS	69.8	54.4	69.4	54.1
Well diff endocrine tumours, carcinoid	64.9	37.2	64.9	37.2
Well diff endocrine tumours, atypical carcinoid	+	+	+	+
Poorly diff endocrine carcinoma lung small cell excluded	**34.9**	**14.9**	**34.7**	**14.8**
Mixed endocrine exocrine carcinoma	50.9	55.4	50.9	55.4
Endocrine carcinoma of Thyroid gland	90.7	82.6	90.7	82.6
Well diff endocrine carcinoma not functioning of Digestive organs	**81.0**	**69.5**	**80.7**	**69.3**
Well diff endocrine carcinoma functioning Pancreas Digest tract	88.8	63.0	87.0	61.6
Endocrine carcinoma of Skin	76.9	48.9	76.9	48.9

+ statistic could not be calculated

Recommendations

The revision had a marginal impact on mesothelioma, liver angiosarcoma, sarcoma and atypical chronic myeloid leukemia estimates. The survival decreased after the revision for all the tumours considered: mesothelioma from 7.2% to 5.5%; liver angiosarcoma from 23% to 19%, GIST from 85% to 68%. The incidence of atypical chronic myeloid leukemia reached 0.02/100,000 and the 5-year survival was estimated to 25%. Before the revision, the limited number of cases didn't allow an adequate estimate of both, incidence and 5-year survival.

The correction of misclassified cases allowed to provide more precise estimates of incidence and survival. In same cases (atypical chronic myeloid leukemia), it allowed to have an estimate previously lucking because of the too limited number of cases.

For the other tumours, the revision had no impact on incidence or survival. The proportion of unspecified morphologies remained high for the majority of the tumours revised. This confirms that a certain proportion of "NOS" cases exists and is related to difficulties in reaching a diagnosis probably due to the health care organisation. An efficient health system is particularly important in dealing with rare cancers because of the difficulty of diagnosis and of the complexity of treatments.

The misclassification problems addressed by this revision focused on quality, completeness of diagnosis and follow-up. Although relevant, the proportion of cases with possible problems of misclassification were often low in the subset of data of the present study. The small proportion of cases revised has to be considered to adequately interpret the small impact of the revision on incidence and survival.

This revision suggested the following recommendations:

- to establish quality check for long-term survivors of CNS tumours (with unspecified diagnosis), mesothelioma and liver angiosarcoma in centralised database such as EUROCARE. High proportion of long survivors should be used as indicator of a problem of quality of diagnosis or/and follow-up that has to be checked by CR;

- to organised periodically revision of cases of long-term survivors of CNS tumours (with unspecified diagnosis), mesothelioma and liver angiosarcoma at CR level or to revise mesothelioma long-term survivors if their proportion is higher than 15% (at CR level)§;

- to further study mesothelioma long-term survivors (including centralised revision of pathological reports and samples);

- to ameliorate the diagnosis of exceptional tumours (such as liver angiosarcoma) supporting a centralised revision of pathological reports;

- to improve the identification of subsite of head and neck cancers on the basis of the information available in the pathological reports;

- to report detailed histology: the morphology with the highest codes ICD-O should always be reported;

- to agree on relevant information, available in the pathological reports, to define the behaviour of carcinoids of the digestive tract;

- to promote and raise awareness on rare cancers and difficulties in diagnosis and registration among clinicians, pathologist and registrars.

Future activities of RARECARE to improve data quality and registration of rare cancers

In collaboration with the European School of Oncology (ESO), the first international course on rare cancers will be held from March 31st to April 1st, 2011 in Italy, Stresa.
The course will be directed to clinicians, epidemiologists, registrars and pathologists. It will aim at describing rare cancers burden and at discussing rare cancers challenges including pathological issues, barriers for research and health care organisation. The course will also provide an overview of epidemiological and clinical information of a selected group of rare cancers.

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Annex

Data quality study: protocol for the data collection

INTRODUCTION

The RARECARE project is aimed at estimating the burden of rare malignant tumours in Europe using the population based cancer registries (CRs) data. One of the major objectives of the project is to improve data quality in rare cancers registration. It is appropriate, therefore, to assess the validity, completeness and standardisation of cancer registries data on rare cancers between registries. The improvement of the quality of data will consequently improve the comparability of incidence, prevalence and survival of rare cancers among European population-based cancer registries.

On the basis of past experience of the analysis of rare cancers [Lancet Oncology, 2006], data quality for rare cancers doesn't seem as good as that for non rare tumours. The major reason is that rare tumour entities, as defined by the RARECARE project, are a combination of ICD-O topography and morphology codes. Sometimes although topography is detailed to the 4th digit (sub-site) and morphology codes refer to a rare morphology, there are well known problems in diagnostic accuracy. An additional difficulty is due to the changes of the ICD-O classifications. The inclusion of new morphology and topography codes has forced registries to update not only the new but also the old data leading to additional efforts and raising comparability issues.

In this context, the main objectives of the RARECARE study are:

- To assess the comparability of data among CRs.
- To assess the validity of CRs data for rare cancers
- To verify the completeness of data on rare cancers.
- To verify the availability of information on stage, treatment and place of treatment.

Because previous experiences demonstrated that the revision of the pathological reports can improve the quality of the morphology and of the topography this study aims at assessing the data quality for rare cancers through the revision of information/reports available at the CRs offices.

This study will focus on the rare tumours of the so called 'short list', a group of rare tumours with high priority. These tumours have been selected because of their relevance for primary prevention, early diagnosis, diagnostic accuracy, quality of care, clinical research feasibility or because of their poor data quality in rare cancer registration.

Rare tumours to be included in the study with their related relevance for primary prevention, early diagnosis, accuracy of diagnosis, availability of treatment and poor data quality in rare cancer registration are listed in Table 1.

Table 1. Rare tumours to be studied for data quality and reasons for their relevance.

Rare tumour	Primary prevention	Early diagnosis	Diagnostic accuracy	Quality of care	Clinical research feasibility	Poor data quality
Mesothelioma	**+++**	?	++	+	++	+
Liver angiosarcoma	**+++**	?	++	++	+	+
Sarcomas	++	++	**+++**	++	+	++
Oral cavity tumours	++	**+++**	+	++	++	+
CNS tumours	++	++	++	**+++**	++	++
Germ cell tumors	+	+	+	**+++**	+	+
Leukaemia	++	+	++	**+++**	+	++
Endocrine tumours	+	?	++	++	++	**+++**

+++ very high relevance, ++ high relevance; + relevant; ? no data on the efficacy

For the revision of the morphology and/or of the primary cancer site, the documents/files to be revised will be the pathologic reports and the clinical dossiers **filed at cancer registry offices**. If necessary and feasible also the revision of the source documents such as medical records available at the hospital will be considered.

Pathological reports will be used also to check the availability of information on the stage of the tumours. The CRs internal dossiers of the case will be reviewed to verify the availability of information on treatment and place of treatment.

The mortality files will be reviewed **only** for mesothelioma, angiosarcoma of the liver and central nervous system tumours in order to check the vital status.

The period of diagnosis of cases to be revised is 1995-2002. The study will focus on malignant tumours only (5^{th} digit of the morphology codes ≥3).

MESOTHELIOMA

The review will focus on long term survivors with ICD-O morphology 9050-9053 of **any sites** and of all cases with pleural cancers that are not coded as mesothelioma.
For this lethal cancer, we expect a very low proportion of cases alive two or more years after diagnosis thus, all the incident cases diagnosed during the study period, alive two (or three) years after the diagnosis have to be checked.

For these cases the revision should:

- confirm the diagnosis, this may be the case for patients surgically treated, or for patients that have undergone multimodal treatment (surgery, plus chemo/radiotherapy)

or

- change the diagnosis specifying the new code if it was a non malignant lesion of the pleura. Actually, pulmonary pleura in asbestos exposed people could be site of nodules, inflammatory pseudo-tumour, atypical adenomatous hyperplasia, etc. Furthermore, the pleura could be site of distant metastasis.

and

- correct the life status of the patient because the death certificate was not correctly linked.

In order to ascertain the completeness of mesothelioma of the pleura, all the pleura non mesothelioma cases have to be checked.

LIVER ANGIOSARCOMA

To identify missing cases, the revision will focus on all liver cancers (topography ICD10 C22.0) microscopically verified and with a morphologic code **different from**:

8160 (cholangiocarcinoma),
8161 (cystadenocarcinoma),
8170 (hepatocellular carcinoma),
8171 (fibrolamellar hepatocellular carcinoma),
8180 (hepato-cholangioma),
9590, 9591 (lymphoma),
8970 (hepatoblastoma),

The above listed cancers are the most frequent usual primary liver cancers and so, with a high degree of probability to be well coded in the database.

The quality of diagnosis and the completeness of incidence will be checked also through the revision of all sarcoma (not otherwise specified) NOS of the liver (only microscopically verified cases).

For these cases the revision should confirm the diagnosis or change the diagnosis reporting the new code. In addition for angiosarcoma long term survivors the life status and the date of end of follow up have to be checked.

SARCOMAS

Diagnosis of sarcoma is difficult. Sometimes the right diagnosis comes after several months since the first unspecific diagnosis of sarcoma or epithelial tumour.

For this exercise, it is suggested to revise all the sarcoma NOS (8800) and the descriptive ICD-O3 morphology codes 8801-8806, of any site (except liver because these cases will be checked as part of the review of the angiosarcoma of the liver). We expect to increase the number of Gastro Intestinal Stromal Tumours (GIST) and of all the new morphology codes included in the ICD-O3. It is worth stressing that it is possible to have a diagnosis of sarcoma NOS, since also expert pathologists may give this diagnosis.

For these cases the revision should confirm the diagnosis or change the diagnosis reporting the new code.

TUMOURS OF ORAL CAVITY

The revision will focus on morphology codes 8000, 8001, 8010, 8011 (carcinoma NOS) for the ICD-O site codes C02.0-02.3, 2.9, 03.0-05.0, 06.0-06.9 (oral cavity) and the unspecific site codes (2.8 and 5.9) in order to distinguish between oral cavity and oropharynx.

It is expected to increase the number of squamous cell carcinoma of the oral cavity.

For these cases the revision should confirm or change **both the morphology and topography codes** specifying the new codes.

CENTRAL NERVOUS SYSTEM TUMOURS

Some of the Central Nervous System (CNS) tumours are characterized by the availability of effective treatment, e.g. selected gliomas, pinealoma, germ-cell tumours, lymphomas etc.

However, several problems such as method and accuracy of diagnosis, high proportion of DCO, incompleteness of incidence, benign/borderline malignancies, etc. can affect the quality of CNS tumours data and the calculation of the epidemiologic indicators.

The review will focus on:

- Long-term survivors with a diagnosis of unspecified morphology codes (8000, 8001, 8010). The review should clarify whether the long-term survivors are brain malignant tumours. In addition the revision should verify if the life status is correct.

- Cases with diagnosis of Glioma NOS (9380), microscopically verified. The review should confirm or change the diagnosis, specifying the new code. If available, the information on grading should be added.

GONADAL GERM CELL TUMOURS

These tumours are characterised by the availability of treatment.

The review will focus on the morphology NOS (8000-8010) cases of the testis (C62, C63.0, C63.1) and of the ovary (C56). ONLY microscopically verified cases will be reviewed.

For these cases the revision should confirm the diagnosis or change the diagnosis reporting the new code.

LEUKAEMIA

Different leukaemias have different prognosis and division into main diagnostic groups is necessary to analyse treatment and prognosis of leukaemia. Therefore the number of unspecified leukaemia cases should be as low as possible. Unspecified codes are: 9801, 9820 and 9860. The two major types of CML: typical (9875) and atypical (9876) have different prognosis, because of the availability of treatment for typical CML. Consequently, also the number of CML, NOS (M9863) should be as low as possible.

The review will focus on:

- all the leukaemias, NOS (9800, 9801, 9820, 9860),
- CML, NOS (ICD-O3 9863)

For these cases the revision should confirm the diagnosis or change the diagnosis reporting the new code.

MALIGNANT DIGESTIVE ENDOCRINE TUMOUR (MDET)

Some registries have difficulties to identify small-cell MDET, which are major prognostic factors (the 5-year relative survival rate being 8% compared to 58% for well-differentiated MDET).
Well differentiated endocrine tumours include the following codes, pancreatic insular carcinoma (8150/3), insulinoma (8151/3), gastrinoma (8153/3), vipoma (8155/3), glucagonoma (8152/3), non secreting endocrine carcinoma (8246/3), (those tumours being pancreatic tumours) and carcinoid (8240, 8241, 8243, 8244/3) which can be found at all digestive site.

Small cell tumours include small cell endocrine carcinoma (8041/3) and oat cell carcinoma (8042/3) (this code is very rarely used). In some registries small cell endocrine tumours are not identified. Their identification may require a review of pathology reports concerning undifferentiated carcinoma (8020/3, 8021/3) of the digestive tract (topography codes C15 to C25). The objective is to find in the pathology reports the term “round” or “fusiform” cells which suggest endocrine tumour. In the case that the terms “round” or “fusiform” are in the reports, the code should be changed in 8041.

High incidence and survival rates of MDET have been related to a high proportion of appendix MDET. These tumours are usually benign suggesting that tumours of undetermined malignancy were recorded among MDET. We invite to review the pathological reports of all carcinoid tumours (8240-8244) in order to distinguish between borderline and malignant. The following criteria should be used to identify the behaviour (These criteria are proposed and have to be used ONLY for this study):

- Invasion of the muscularis propria
- Dimension of the tumour
- Proliferation index (Ki67)

The behaviour is equal to 3 if:

- the tumour invades the muscularis propria (stomach, small intestine and colon and rectum), invades the visceral peritoneum (appendix), has an extra-pancreatic extension (pancreas); **AND**
- the size is more than 1 cm (stomach and small intestine) or more than 2 cm (large intestine, appendix and pancreas).

Additional information confirming the malignant behaviour are:

- mitotic index 2 to 10;
- proliferation index (Ki67) 2 to 15%;
- angioinvasion.

Please refer to Table 2 for more details.

The revision will focus on the topography codes: C16-25

Table 2. Criteria to identify the behaviour of endocrine tumours (ET) (in situ *vs* malignant).
(These criteria are proposed and have to be used ONLY for this study)

	Well differentiated benign and borderline ET	**Well differentiated endocrine carcinoma**	**Undifferentiated endocrine carcinoma**
Differentiation	Well differentiated	Well differentiated	Undifferentiated
Angioinvasion	No	Possible	Possible
Size	Stomach, Small intestine: ≤ 1cm Appendix, colon, rectum : ≤ 2 cm Pancreas : < 2 cm	Stomach, Small intestine : >1 cm Appendix, colon, rectum : > 2 cm Pancreas : >2 cm	
Mitotic Index	≤ 2	2 to 10	> 10
Proliferation Index (Ki67)	≤ 2 %	2 to 15 %	> 15 %
Local invasion	Digestive tumour : mucosae/submucosae Pancreas : intra-pancreatic	Digestive tumour (out appendix): > Muscularis propria Appendix : invasion of the visceral peritoneum Pancreas : extra-pancreatic extension	
Metastases	no	Possible	Possible
	Behaviour: /1	/3	/3

For all these rare tumours the revision have to specify whether information of stage, treatment and place of diagnosis and treatment are available.